#6

PATENT
Attorney Docket No.07681.0010-01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1632
CAMPBELL et al.	Examiner: D. Crouch
Serial No.: 09/650,194	
Filed: August 29, 2000	
For: UNACTIVATED OOCYTES AS CYTOPLAST RECIPIENTS FOR NUCLEAR TRANSFER	

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

REQUEST UNDER 37 C.F.R. § 1.607 FOR INTERFERENCE WITH U.S. PATENT 5,945,577 TO STICE ET AL.

Pursuant to the provisions of 37 C.F.R. §1.607, applicants respectfully request that an interference be declared between claims 19-50 in the subject application and claims 1-24 of U.S. Patent 5,945,577 to Stice et al. The patent is hereinafter referred to as "the Stice patent". A copy is attached as Exhibit A.

Applicants submit the following information in fulfillment of the requirements of 37 C.F.R. § 1.607.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

I. PROPOSED COUNT

In fulfillment of the requirement of Rule 1.607(a)(2), applicants propose the following Count for purposes of interference:

A method of cloning a non-human mammal by nuclear transfer comprising:

(i) inserting a nucleus of a cultured diploid non-human mammalian fibroblast in the G1 phase of the cell cycle into an unactivated, enucleated metaphase II-arrested non-human mammalian oocyte of the same species to reconstruct an embryo;
(ii) maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term;
(iii) activating the resultant reconstructed embryo;
(iv) culturing said activated, reconstructed embryo to blastocyst; and
(v) transferring said cultured, reconstructed embryo to a host non-human mammal of the same species such that the reconstructed embryo develops to term;

or:

A method of cloning a non-human mammal by nuclear transfer comprising the following steps:

(i) inserting a desired non-human mammalian proliferating somatic cell that has been expanded in culture, or a nucleus isolated from said somatic cell, into a non-human mammalian enucleated oocyte of the same species under conditions suitable for the formation of a nuclear transfer (NT) unit;
(ii) activating the resultant nuclear transfer unit;
(iii) culturing said activated NT unit until greater than the 2-cell developmental stage; and
(iv) transferring said cultured NT unit to a host non-human mammal of the same species such that the NT develops in to a non-human mammal;

wherein the donor cell or donor cell nucleus is from a fibroblast.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The proposed Count incorporates the exact language of applicants' claim 35. The proposed Count also incorporates the exact language of claim 11, as it depends from claim 3, of the Stice patent.

For many years it was a requirement in interference practice that a count should not be narrower in scope than any patent claim or any application claim that is patentable over the prior art and designated to correspond to the count at the time the interference was initially declared. See 37 C.F.R. § 1.606. This requirement was recently eliminated. *See* 65 Fed. Reg. 70,489 (November 24, 2000). The proposed Count follows the new practice in that it is not as broad as the broadest claim in the Stice patent and is not as broad as applicants' broadest claim.

II. IDENTIFICATION OF PATENT CLAIMS CORRESPONDING TO THE PROPOSED COUNT

Claims 1-24 of the Stice patent, which are all of the claims of the patent, are directed to methods of cloning non-human mammals and non-human mammalian fetuses. All of the patent claims are directed to the same invention and should be designated as corresponding to the proposed Count. *See* 37 C.F.R. § 1.606.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

III. IDENTIFICATION OF APPLICANTS' CLAIMS CORRESPONDING TO THE PROPOSED COUNT

Applicants' claims 19-50 are also directed to methods of cloning non-human mammals and non-human mammalian fetuses. All of these claims should be designated as corresponding to the proposed Count.

IV. APPLICATION OF APPLICANTS' CLAIMS TO THE DISCLOSURE IN THEIR APPLICATION

Applicants' claims 19-50 were presented in a Preliminary Amendment filed in the subject application. Section (a)(5) of Rule 1.607 requires applicants to identify support in their application for any of their claims designated as corresponding to the proposed Count.

Exhibit B annexed hereto contains the recitations in each of applicants' claims and quotations from the specification supporting each recitation. Exhibit B thus satisfies the requirement of Rule 1.607(a)(5).

V. APPLICANTS ARE THE SENIOR PARTY RELATIVE TO STICE ET AL.

The Stice patent is based on a U.S. application filed January 10, 1997. Stice et al. did not claim the benefit of any earlier-filed applications. Thus, Stice et al.'s effective filing date for purposes of an interference is January 10, 1997.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants, on the other hand, have an effective U.S. filing date of August 31, 1995, through a series of priority applications. Specifically, the subject application is a continuation of parent application Serial No. 08/803,165. Thus, applicants are entitled to the benefit of the filing date of February 19, 1997, of the parent application. 35 U.S.C. § 120

The parent application, in turn, is a §371 application of PCT/GB96/02098, filed August 30, 1996. A copy of the PCT application as published under No. WO 97/07668 is attached as Exhibit C. The PCT application and the subject application are identical. Thus, applicants are also entitled to the benefit of the filing date of August 30, 1996 of the PCT application. 35 U.S.C. § 119 and MPEP 1896.

Finally, the PCT application claims the benefit of British application No. 95 177796, filed August 31, 1995. A certified copy of the British priority application is attached as Exhibit D.

There are several differences between the British priority application and the subject U.S. application. These differences have been highlighted on Exhibit E, which is a copy of the subject application. It will be evident that the highlighted passages do not affect applicants' right to the benefit of the British application for the subject matter of claims 19-50 in the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

subject application. Thus, applicants are entitled to the filing date of their British priority application. 35 U.S.C. § 119.

In summary, applicants effective filing date of August 31, 1995, can be traced from the subject continuation application through the parent application to the earlier PCT application and finally to the British priority application. Because applicants' effective filing date of **August 31, 1995**, predates by **almost 17 months** Stice et al.'s effective filing date of **January 10, 1997**, justice requires that applicants be named the senior party in any interference that may be declared with the Stice patent.

VI. APPLICANTS AND STICE ET AL. ARE CLAIMING THE SAME PATENTABLE INVENTION

Applicants' claims 19-50 define the same patentable invention as claims 1-24 in the Stice patent. Thus, interference-in-fact exists. *See* 37 C.F.R. § 1.601(j). ("An interference-in-fact exists when at least one claim of a party that is designated to correspond to a count and at least one claim of an opponent that is designated to correspond to the count define the same patentable invention.")

More particularly, 37 C.F.R. § 1.601(n) provides that one invention is "the same patentable invention" as another invention when the first invention is the same as (35 U.S.C. § 102) or is obvious (35 U.S.C. § 103) in view of the second invention,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

assuming the second invention is prior art with respect to the first invention.

Recent precedent of the Trial Section of the Interference Division of the Board of Patent Appeals and Interferences indicates that resolution of whether an interference-in-fact exists involves a two-way patentability analysis. According to the Board:

> The claimed invention of Party A is presumed to be prior art vis-a-vis Party B and vice versa. The claimed invention of Party A must anticipate or render obvious the claimed invention of Party B and the claimed invention of Party B must anticipate or render obvious the claimed invention of Party A. When the two-way analysis is applied, then regardless of who ultimately prevails on the issue of priority, * * * [USPTO] assures itself that it will not issue two patents to the same patentable invention.

Winter v. Fujita, 53 U.S.P.Q.2d 1234, 1243 (Bd. Pat. App. & Intf. 1999), reh'g denied, 53 U.S.P.Q.2d 1478 (Bd. Pat. App. & Intf. 2000).

In support of their request for declaration of an interference, applicants will describe their invention and then compare the terms in Stice et al.'s claim 11, as it depends from claim 3 of the Stice patent, with the corresponding terms in applicants' claim 35. This comparison will convincingly show that applicants are claiming the same patentable invention as that claimed in the Stice patent and that interference-in-fact exists.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants will then show that applicants have met the one year time limit imposed by 35 U.S.C. § 135(b) by claiming this invention within one year of the issuance of the Stice patent.

A. APPLICANTS' PIONEERING WORK INVOLVING NUCLEAR TRANSFER INTO DIFFERENTIATED CELLS LEAD TO THE CLONING OF "DOLLY" THE SHEEP

The report of the cloning of "Dolly" the sheep generated enormous attention in the scientific and general press because of its novelty and the significance of the work. This cloning work is the subject of applicants' invention.

At the time of applicants' invention, animal cloning had been achieved by genetic manipulation using nuclear transfer technology: A nucleus was removed from a donor cell, then transplanted into an oocyte whose own nucleus had previously been removed. The resulting renucleated oocyte gave rise to an animal that carried the nuclear genome of only the donor of the nucleus. The individual providing the donor nucleus and the individual that developed from the renucleated oocyte were referred to as "clones".

Nuclear transfer technology first employed a donor cell that was derived from an early embryo. The cells of the embryo had not undergone substantial division and differentiation --- the cells were totipotent, meaning that they had the potential to develop into any type of cell in an adult.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Unlike embryo cloning, the prospect of cloning a cell from an adult seemed remote. More particularly, all animals develop from a single cell, the fertilized ovum, which gives rise to the various tissues and organs. Cells from the ovum undergo division and differentiation, which is driven by gene switching: The difference between one cell type and another is primarily in the range of genes that are active in each cell. Certain genes in the genome are "programmed" to express their proteins, leading to cell specialization at a very early stage of development within the embryo.

It was thought that a differentiated cell was committed to a specialized course of development and ultimately a specialized function. It was believed that a differentiated cell exhibited a memory for its specialized function and passed its functional characteristics on to its progeny. Prior to applicants' invention, is it was thought that once a cell became differentiated and entered a determined developmental pathway, the pathway was irreversible. No manipulation of the cell environment would, for example, cause a heart cell to differentiate into a liver cell.

Applicants' specification describes the cause of this phenomenon as follows: "During development certain genes become 'imprinted' i.e., are altered such that they are no longer transcribed." (Specification at page 4, lines 16-18.)

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Applicants discovered that the "imprint" on an adult differentiated cell can indeed be removed by "reprogramming" the cell nucleus following its transfer to the enucleated, recipient oocyte. The application of this discovery produced "Dolly" the sheep in Example 2 in the subject application by nuclear transfer from an adult differentiated cell in the G_o phase of the cell cycle.

More particularly, as described in the present application, the nucleus that is transferred to the enucleated, recipient oocyte can be taken from an adult differentiated cell. "Dolly" the sheep was produced in Example 2 using a nucleus from an adult sheep cell in the G_o phase of its cell cycle. The specification teaches that an adult differentiated cell in the G_1 phase of its cell cycle could be used as well. (See pages 19-22, *infra*, for a more detailed discussion of the cell cycle.) Nuclear transfer from the adult differentiated cell into an oocyte arrested in metaphase II gave rise to a viable sheep embryo by maintaining normal ploidy (i.e. diploidy). Activating the embryo after nuclear transfer allowed the nucleus to remain exposed to the recipient cytoplasm. As explained in greater detail on pages 29-31, *infra.*, this delay resulted in nuclear reprogramming so that the renucleated oocyte could be implanted in a live animal and could develop to term.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The successful cloning of "Dolly" showed, for the first time, that the nucleus from a differentiated adult cell could be reprogrammed to become totipotent once more, just like the genetic material in the fertilized oocyte from which the donor cell had ultimately developed. This successful cloning of an adult animal forced scientists to accept that genome modifications, once considered irreversible, can be reversed, and that genomes of adult cells can be reprogrammed by factors in the oocyte to make them capable once again of differentiating into any cell type.

All of applicants' claims are directed to a method of cloning a non-human mammal by nuclear transfer using a differentiated cell from an adult donor.

2. **Stice et al. also claim to have invented animal cloning by nuclear transfer using differentiated cells**

The Stice patent also claims a method of cloning a non-human mammal by nuclear transfer using a differentiated cell. Stice et al. describe their work as follows:

> According to the invention, cell nuclei derived from differentiated fetal or adult, mammalian cells are transplanted into enucleated mammalian oocytes of the same species as the donor nuclei. The nuclei are reprogrammed to direct the development of cloned embryos, which can then be transferred into recipient females to produce fetuses and offspring, or used to produce CICM cells. The cloned embryos can also be combined with fertilized embryos to produce chimeric embryos, fetuses and/or offspring.

(Exhibit A at col. 6, lines 3-11).

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The importance of differentiated cells for nuclear transfer is pointedly emphasized in the Stice patent: "Again the present invention is novel because differentiated cell types are used." (Exhibit A at col. 8, lines 31-32.)

Several times during prosecution, Stice et al. again emphasized that the essence of their work was the use of differentiated cells in nuclear transfer. For example, in an Amendment filed in response to a § 112, first paragraph, enablement rejection, Stice et al. stated:

> Rather, as discussed above, the present invention involves the generic discovery that cells committed to a somatic cell lineage or somatic cells or nuclei derived therefrom which are capable of division may be used as nuclear transfer donors during nuclear transplantation, and give rise to cloned non-human mammalian embryos, fetuses, and offspring.

(Exhibit F at 11.) The "cells committed to a somatic cell lineage . . . which are capable of division", referred to by Stice et al., are differentiated cells.

Stice et al. stated in the same paper that none of the particular steps in the cloning process were critical to the efficacy of their invention. *Id.* The use of a differentiated cell in animal cloning was the essence of their work. Stice et al. were apparently unaware of applicants' work using differentiated cells in nuclear transfer when Stice et al. filed their application.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

C. Applicants' Claimed Invention Is the Same as the Subject Matter of the Stice et al. as Shown by a Comparison of Applicants' Claim 35 with Claim 11 of the Stice Patent as it Depends from Claim 3 of the Patent.

Table 2 and the comments that follow show that applicants' claim 35 contains limitations that are the same as limitations in claim 11 as it depends from claim 3 of the Stice patent. These are the two claims that comprise applicants' Proposed Count on pages 2-3, *supra*.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

TABLE 2

COMPARISON OF APPLICANTS' CLAIM 35 WITH CLAIM 11 OF THE STICE PATENT AS IT DEPENDS FROM CLAIM 3 OF THE PATENT

Campbell et al. claim 35	Claim 11, of the Stice patent, as it depends from claim 3
35. A method of cloning	3. A method of cloning
a non-human mammal	a non-human mammal
by nuclear transfer	by nuclear transfer
comprising:	comprising the following steps:
(i) inserting	(i) inserting
a nucleus	a . . . nucleus[1]
of a cultured	[of a] cell that has been expanded in culture
diploid	
non-human	non-human
mammalian	mammalian
fibroblast	**fibroblast** (claim 11)
in the G1 phase of the cell cycle	proliferating
into	into
an unactivated	
enucleated	enucleated
metaphase II-arrested	
non-human	non-human
mammalian	mammalian
oocyte	oocyte
of the same species	of the same species
to reconstruct an embryo;	

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Campbell et al. claim 35	Claim 11, of the Stice patent, as it depends from claim 3
(ii) maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term;	under conditions suitable for the formation of a nuclear transfer (NT) unit;
(iii) activating the resultant reconstructed embryo;	(ii) activating the resultant nuclear transfer unit;
(iv) culturing said activated, reconstructed embryo	(iii) culturing said activated NT unit
to blastocyst; and	until greater than the 2-cell developmental stage; and
(v) transferring	(iv) transferring
said cultured, reconstructed embryo	said cultured NT unit
to a host	to a host
non-human	non-human
mammal	mammal
of the same species	of the same species
such that the reconstructed embryo develops to term.	such that the NT develops in to a non-human mammal.

[1] The complete clauses of Stice claim 3 read as follows: "inserting a desired non-human mammalian proliferating somatic cell that has been expanded in culture, or a nucleus isolated from said somatic cell, into a non-human mammalian enucleated oocyte of the same species. . . ." (Exhibit A at col. 18, lines 62-66.)

The recitation of a "fibroblast" is emphasized in Table 2 to highlight that applicants and Stice et al. are each claiming a method of nuclear transfer using a differentiated cell. That is, a fibroblast is a differentiated cell.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

It will be evident from Table 2 that applicants' claim 35 contains recitations that are identical to claim 11 of the Stice patent as it depends from claim 3. As described in Exhibit B, Table 1, attached hereto, all of these recitations are supported by applicants' specification. Support for these recitations in applicants claims will not be further discussed.

Instead, the terms in applicants' claim that are absent from Stice et al.'s claim, or appear to be different, will now be discussed. These terms are arranged below in a different order than they appear in Table 2 to facilitate an understanding of the meaning of the terms and their relation to each other. This discussion will leave no doubt that applicants and Stice et al. are claiming the same invention and that interference-in-fact exists.

(a) The recitation of "in the G1 phase of the cell cycle" in applicants' claim versus "proliferating" in Stice et al.'s claim

The nucleus for cloning an animal is taken from a differentiated cell under certain conditions recited in the claims. Specifically, in applicants' claim, the nucleus is taken from a fibroblast "in the G1 phase of the cell cycle". Stice et al. use a "proliferating" fibroblast that has been expanded in culture.

Somatic cells in culture are replicating in the mitotic cell cycle. Thus, underlying the meaning of the expression "in the G1

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

phase of the cell cycle" in applicants' claim and the term "proliferating" in Stice et al.'s claim is an understanding of this cell cycle and an appreciation for the limited number of phases in the cycle. The mitotic cell cycle is described in applicants' specification as follows.

The mitotic cell cycle has four distinct phases, G1, S, G2, and M. The beginning event in the cell cycle, called start, takes place in the G1 phase and has a unique function. The decision or commitment to undergo another cell cycle is made at start. Once a cell has passed through start, it passes through the remainder of the G1 phase, which is the pre-DNA synthesis phase.

The second stage, the S phase, is when DNA synthesis takes place. This is followed by the G2 phase, which is the period between DNA synthesis and mitosis. Mitosis itself occurs at the M phase. Quiescent cells (which include cells in which quiescence has been induced as well as those cells which are naturally quiescent, such as certain fully differentiated cells) are generally regarded as not being in any of these four phases of the cycle; they are usually described as being in a G0 state, so as to indicate that they would not normally progress through the cycle. (Applicants' specification at page 7, line 26 to page 8, line 11.)

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

It is evident from this description that there are only four phases in the cell cycle of a somatic cell. During prosecution of the Stice et al. patent, the Examiner indicated that the expression "proliferating somatic cell that has been expanded in culture" embraced these four cycles. *See* Exhibit G at page 6, paragraph 4: "Proliferating cells are non-quiescent cells, and are in cell cycle stage M, G1, S, or G2." Thus, the scope of the Stice et al. claim is established by its prosecution history.

In applicants' claim 35, the nucleus selected for transfer to the enucleated oocyte is taken from a fibroblast in "the G1 phase." Claim 11, as it depends from claim 3, of the Stice patent contemplates the use of a proliferating somatic cell at any phase of its cell cycle, namely, G1, S, G2, or M.

Applying the analysis required by 37 C.F.R. §1.601(n), applicants' species "in the G1 phase" anticipates the Stice et al. claim embracing only four phases, which include "the G1 phase," assuming applicants' claim is prior art to Stice et al.'s claim and all of the other claim limitations are the same. A later genus claim is never patentable over an earlier species claim. *Eli Lilly v. Barr Laboratories, Inc.*, 222 F.3d 973, 976 (Fed. Cir. 2000).

Following a similar analysis, but assuming the Stice et al. claim is prior art to applicants' claim, applicants' claim to the use of a fibroblast in the G1 phase would be rendered *prima facie*

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

obvious by Stice et al.'s claim encompassing the use of a fibroblast in one of the G1, S, G2, or M phases of the cell cycle. Indeed, applicants' claim to one phase of the cell cycle may be anticipated by Stice et al.'s claim embracing only four phases, one of which is recited in applicants' claim, because it is well established that a small genus can anticipate a species within that genus. *See, e.g., In re Petering*, 301 F.2d 676, 682, 133 U.S.P.Q. 275, 280 (C.C.P.A. 1962) (Genus of 20 compounds describes each species within the meaning of § 102(b)); *In re Schaumann*, 572 F.2d 312, 316-317, 197 U.S.P.Q. 5, 9 (C.C.P.A. 1978) (Prior art disclosure embraces such a limited number of compounds closely related to one another in structure that it "provides a description of those compounds just as surely as if they were identified in the reference by name.").

In any event, the recitation of a somatic cell "in the G1 phase of the cell cycle" in applicants' claim and the recitation of a "proliferating" somatic cell in Stice et al.'s claim do not impart patentable distinctness to either claim. One claim anticipates the other claim, while the other claim at the least renders the first claim *prima facie* obvious.

(b) The recitation of "diploid" in applicants' claim

The fibroblast cell from which the nucleus is taken for transfer to the enucleated oocyte is "diploid" in applicants'

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

claim. This recitation is inherent in applicants' recitation of a fibroblast "in the G1 phase of the cell cycle." A fibroblast "in the G1 phase of the cell cycle" is "diploid".

The recitation of "diploid" is absent from Stice et al.'s claim, but the absence of this limitation is immaterial. Indeed, the ploidy of a cell in the somatic cell cycle is inherent in the phase of the cycle. According to Stice et al., there is no significance to the phase of the cell cycle during which the fibroblast nucleus is taken for transplantation: "The fibroblast cells can be isolated at virtually any time in development . . . ." (Exhibit A, at col. 16, lines 12-13). Since ploidy is a function of the stage of the cell cycle and the fibroblast can be isolated at any stage, it necessarily follows that ploidy is of no significance in the nuclear transfer method of Stice et al.

The recitation of the ploidy of the fibroblast does not change the analysis in section (a), *supra*. If claims reciting a fibroblast "in the G1 phase of the cell cycle" or a "proliferating" fibroblast are not patentably distinct, reciting the ploidy of the cell, which is inherent in the phase of the cell cycle, does not make the claims patentably distinct.

(c) The recitation of "metaphase II - arrested" in applicants' claim

Applicants' claim contains another recitation that is absent from Stice et al.'s claims, namely, that the oocyte into which

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

the nucleus from the fibroblast is transferred is in a particular phase of its cell cycle. It is "metaphase II-arrested." The absence of this term from Stice et al.'s claim is immaterial for determining "same patentable invention" under Rule 1.601(n).

Stice et al. teach in their specification that metaphase-II oocytes should be used for successful nuclear transfer. Specifically, Stice et al. state that:

> Additionally, metaphase II stage oocytes, which have been matured *in vivo* have been successfully used in nuclear transfer techniques.
>
> * * *
>
> The stage of maturation of the oocyte at nucleation and nuclear transfer has been reported to be significant to the success of NT methods. (See e.g., Prather et al., Differentiation, 48, 1-8, 1991). In general, successful mammalian embryo cloning practices use the metaphase II stage oocyte as the recipient oocyte because at this stage it is believed that the oocyte can be or is sufficiently "activated" to treat the introduced nucleus as it does a fertilizing sperm.

(Exhibit A at col. 8, line 59 to col. 9, line 6.)

According to Stice et al., oocytes in metaphase II are the cells of choice to ensure successful nuclear transfer. Moreover, Stice et al. indicate this was known in the art.

The identification of a "metaphase II-arrested" oocyte as the recipient of the nucleus from the fibroblast in applicants' claim and the absence of this recitation from Stice et al.'s claim does not impart separate patentability to either claim applying the analysis under Rule 1.601(n). Specifically,

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

assuming applicants' claim is prior art to Stice et al.'s claim and all of the other claim limitations are the same, applicants' claim would anticipate the claim of Stice et al.; applicants' claim would contain all of the limitations of the claim of Stice et al., and the additional limitation "metaphase II-arrested" oocyte in applicants' claim would not change the analysis.

Applying the test in reverse and assuming the Stice et al. claim is prior art to applicants' claim and that all of the other limitations are the same, the recitation of a "metaphase II-arrested" oocyte in applicants' claim would have been obvious in view of the Stice et al. claim taken in view of the knowledge in the art that a metaphase II oocyte was the cell of choice for nuclear transfer.

(d) The recitation of a "reconstructed embryo" in applicants' claim versus "a nuclear transfer (NT) unit" in Stice et al.'s claim

Nuclear transfer or nuclear transplantation were known in the art prior to applicants' invention. These techniques involve the removal of a nucleus from a donor cell and transfer of the nucleus into an oocyte whose own nucleus has been removed. The resulting renucleated oocyte is referred to as a "reconstructed embryo" in applicants' claim and "a nuclear transfer (NT) unit" in Stice et al.'s claim. It is evident from their respective disclosures that there is no patentable difference in these terms.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

Specifically, applicants refer in their specification to the "reconstruction of mammalian embryos by the transfer of a donor nucleus to an enucleated oocyte" (page 1, lines 9-10), and to "[e]mbryo reconstruction by nuclear transfer" (page 1, line 18). These passages are exemplary of those that provide antecedent basis for the recitation of a "reconstructed embryo" in applicants' claim.

Stice et al. used the terms nuclear transfer, nuclear transplantation, and NT interchangeably. (Exhibit A at col. 5, line 66 to col. 6, line 2). Stice et al. described the formation of a NT unit as involving:

> . . . [i]nserting a desired differentiated mammalian cell . . . nucleus into an enucleated mammalian oocyte . . . for the formation of a nuclear transfer (NT) unit . . . .

(Exhibit A at col. 5, lines 21-25.)

It is evident that applicants and Stice et al. are each describing a renucleated oocyte formed by transfer of a nucleus from a differentiated cell even though they use slightly different terminology. Once again the difference in terminology is immaterial and does not alter the analysis under Rule 1.601(n) or the conclusion that the different terminology does not make the claimed subject matter separately patentable.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(e) The recitation of "to reconstruct an embryo" in applicants' claim

Applicants' claim recites that the nucleus from the fibroblast cell is inserted into the enucleated oocyte "to reconstruct an embryo". This recitation was included in the claim to specifically identify the product obtained from the nuclear transfer step.

The claim of Stice et al. does not recite "to reconstruct an embryo". Nevertheless, inherent in the Stice et al. claim is "the formation of a nuclear transfer (NT) unit" as a result of the insertion of the nucleus of the fibroblast into the enucleated oocyte.

The recitation of "to reconstruct an embryo" does not impart separate patentability to applicants' claim under a Rule 1.601(n) analysis, nor does the absence of the corresponding term from Stice et al.'s claim impart separate patentability to their claim, since the limitation is inherent in the nuclear transfer step specifically recited in the claim of Stice et al.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(f) The recitation of

"maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term"

vs.

"under conditions suitable for the formation of a nuclear transfer (NT) unit"

It will be evident from the description of applicants' invention that reprogramming of the nucleus from the fibroblast is an essential step. In terms of the limitations in applicants' claims, this is achieved by "maintaining the reconstructed embryo without activation for a sufficient time to allow the reconstructed embryo to become capable of developing to term." It is during this delay in activation that reprogramming occurs and the "imprint" on the nucleus from the fibroblast is erased.

Stice et al. also describe the need for reprogramming the nucleus from the differentiated cell:

> According to the invention, cell nuclei derived from differentiated fetal or adult, mammalian cells are transplanted into enucleated mammalian oocytes of the same species as the donor nuclei. The nuclei are reprogrammed to direct the development of cloned embryos, which can then be transferred into recipient females to produce fetuses and offspring, or used to produce CICM cells.

(Exhibit A at col. 6, lines 3-9)

Stice et al. then describe the activation step, during which reprogramming occurs, as follows:

LAW OFFICES
FINNEGAN, HENDERSON, FARABOW, GARRETT, & DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

> Preferably, the mammalian cell and oocyte are electrofused in a 500 μm chamber by application of an electrical pulse of 90-120 V for about 15 μsec, about 24 hours after initiation of oocyte maturation. After fusion, the resultant fused NT units are then placed in a suitable medium until activation, e.g., CR1 aa medium. Typically activation will be effected shortly thereafter, typically less than 24 hours later, and preferably about 4-9 hours later.
>
> * * *
>
> In one embodiment, NT activation is effected by briefly exposing the fused NT unit to a TL-HEPES medium containing 6 μm ionomycin and 1 mg/ml BSA, followed by washing in TL-HEPES containing 30 mg/ml BSA within about 24 hours after fusion, and preferably about 4 to 9 hours after fusion.

(Exhibit A at col. 10, lines 16-24 and lines 60-65.)

It is evident from these teachings what Stice et al. intended by the limitation "conditions suitable for the formation of the nuclear transfer (NT) unit" in their claim. The NT unit is activated, after a period of delay, for a period of preferably about 4-9 hours after the nucleus from the fibroblast is transferred to the oocyte.

In summary, applicants and Stice et al. each provide a period for reprogramming the transferred nucleus. Each describes this period in functional terms in their respective claims. The difference in terminology does not impart separate patentability to the claims. The result is the same in each case.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

(g) The recitation of "unactivated" in applicants' claim

Following transfer of the nucleus from the fibroblast into the enucleated oocyte and reprogramming of the genes of the donor nucleus, the resulting renucleated oocyte is activated to resume embryonic development. Applicants and Stice et al. each require a step of "activating" the resulting reconstructed embryo or NT unit in their claims.

Applicants' claim also recites that the enucleated oocyte is "unactivated" at the time of the nucleus is transferred from the fibroblast. While the term "unactivated" is not recited in Stice et al.'s claim, it is inherent in the claim as the claim requires "activating the resultant reconstructed embryo." If the oocyte had already been activated, this activation step would be unnecessary.

In addition, if the oocyte had already been activated, the claim of Stice et al. should have included a step of interrupting activation in order to give meaning to the subsequent step of "activating" the resultant renucleated oocyte. The Stice et al. claim does not include a step of interrupting activation of an activated oocyte, and accordingly, the only reasonable interpretation of the claim is that the oocyte is "unactivated" when the nucleus is transferred.

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The term "unactivated" oocyte, which is inherent in Stice et al.'s claim, does not patentably distinguish the claim from applicants' claim, or vice versa.

(h) The recitation of culturing the renucleated embryo "to blastocyst" in applicants' claim" versus "until greater than 2-cell developmental stage" in Stice et al.'s claim

After the nucleus from the fibroblast has been transferred to the enucleated oocyte to form the reconstructed embryo or the NT unit, and the embryo has been reprogrammed and activated, the embryo is then cultured. In applicants' claim, the reconstructed embryo is cultured "to blastocyst", whereas in Stice et al.'s claim the embryo is cultured "until greater than the 2-cell developmental stage". This is another difference that does not impart patentable distinctness to either claim.

Expansion of an embryo "to blastocyst" generally involves about 32-cell developmental stage. Thus, culturing the reconstructed embryo to blastocyst is within the range of "until greater than the 2-cell developmental stage" in the Stice et al. claim.

Carrying out the analysis under Rule 1.601(n) and assuming all of the other claim limitations are the same, applicants' claim to culturing the reconstructed embryo "to blastocyst" would anticipate Stice et al.'s claim to culturing the embryo "until greater than the 2-cell developmental stage", since the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

limitation in applicants' claim falls within the broader range of Stice et al.'s claim. See, *Eli Lilly, supra*.

Neither applicants nor Stice et al. have indicated in their respective disclosures that there is any criticality to culturing "to blastocyst" or culturing "until greater than the 2-cell developmental stage." Thus, carrying out the analysis Rule 1.601(n) in reverse with the Stice et al. claim being prior art to applicants' claim, it is believed that applicants' claim to culturing the reconstructed embryo "to blastocyst" would be *prima facie* obvious in view of the Stice et al. claim of culturing the embryo "until greater than the 2-cell developmental stage" because the claim limitations overlap and there is no apparent difference in the result obtained using either condition.

(i) The recitation of "such that the reconstructed embryo develops to term" in applicants' claim versus "such that the NT [unit] develops into a non-human mammal" in Stice et al.'s claim

To complete the cloning process, the embryo is transferred to a nonhuman mammal where it is allowed to develop. Applicants' claim recites that "the reconstructed embryo develops to term." The Stice et al. claim recites that "the NT [unit] develops in to a non-human mammal." Once again, these semantic differences are immaterial for purposes of separate patentability under Rule 1.601(n).

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

The Stice et al. claim requiring that "the NT [unit] develops in to a non-human mammal" implies that a live birth occurs, whereas applicants' claim only requires that "the reconstructed embryo develops to term," which implies the full development of a fetus, but not necessarily a live birth.

Before the "NT develops in to a non-human mammal", the NT would have had to develop to term as recited in applicants' claim. Thus, under the analysis of Rule 1.601(n), assuming all of the other claim limitations are the same, the Stice et al. claim to a live birth would anticipate applicants' claim to the development of the embryo "to term" because the Stice et al. process would have produced an embryo that developed to term before the live birth.

Interestingly, in none of the examples in the Stice et al. patent was a live birth described. Only partially developed embryos were reported. Thus, applying the Rule 1.601(n) analysis in reverse leads to a similar conclusion on the lack of separate patentability. Applicants' claim reciting development to term would render obvious the Stice et al. claim reciting development into a non-human mammal assuming all of the other claim limitations were the same.

Thus, once again applying the analysis of Rule 1.601(n), the expression "such that the reconstructed embryo develops to term" in applicants' claim and the recitation "such that the NT

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

develops in to a non-human mammal" in the Stice et al. claim do not impart separate patentability to either claim.

In summary, the comparison of applicants' claim 35 with claim 11 as it depends from claim 3 of the Stice et al. patent shows that most of the claim limitations are identical and those that are not do not impart separate patentability to either claim. The only conclusion is that these two claims define the same patentable invention.

E. APPLICANTS HAVE MET THE ONE YEAR TIME LIMIT IMPOSED BY 35 U.S.C. § 135(b) BY CLAIMING THE SAME PATENTABLE INVENTION AS STICE ET AL. WITHIN ONE YEAR AFTER THE STICE PATENT ISSUED

The Stice et al. patent issued on **August 31, 1999.** Applicants presented claims 19 to 50 in the subject application in a Preliminary Amendment filed **August 29, 2000.**

Applicants thus claimed the interfering subject matter within one year after the Stice patent issued, thereby meeting the one-year time limit imposed by 35 U.S.C. § 135(b).

VII. CONCLUSION

It is a fundamental principle that issuance of two patents for inventions that are either identical to or not patentably distinct from each other must be avoided. M.P.E.P. 2306, *citing Aelony v. Arni*, 547 F.2d 566, 192 U.S.P.Q. 486 (C.C.P.A. 1997). This mandate has a matter of urgency attached to it in the

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000

present case in which a patent has already been issued to an entity that would be the junior party in an interference with applicants. An interference should be declared, and applicants should be designated as the senior party in the interference.

If there are any fees due in connection with the filing of this Request, please charge such fees to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: April 13, 2001

By: _____

Kenneth J. Meyers
Reg. No. 25,146
Tel: (202) 408-4000
Fax: (202) 408-4400
Email: ken.meyers@finnegan.com

LAW OFFICES
FINNEGAN, HENDERSON,
FARABOW, GARRETT,
& DUNNER, L.L.P.
1300 I STREET, N. W.
WASHINGTON, DC 20005
202-408-4000